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A

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6) Documents cited

Nature 1982, 299, 178-180

8) Field of search

C3H

1) Applicant

National Research

Development Corporation

(United Kingdom),

101 Newington

Causeway, London

SE1 6BU

2) Inventors

George Gow Brownlee,

Kong Hong Choo

4) Agent and/or Address for Service

R. K. Percy,

Patent Department,

National Research

Development

Corporation, 101

Newington Causeway,

London SE1 6BU

(54) Genetic engineering

(57) It has been a problem to find an alternative, less time-consuming, and more reliable source of factor IX, a polypeptide which is essential to the human blood-clotting process and necessary for the treatment of patients with Christmas disease. In order to aid in the solution of the problem, there is provided recombinant DNA containing a DNA sequence occurring in the human factor IX genome, and includes recombinant DNA comprising substantially the whole sequence of human factor IX genome, which is

inserted in a cloning vehicle and transformed into a host, such as *Escherichia coli*. Other fragments of the sequence have also been used and the invention includes DNA molecules comprising part or all of human factor IX DNA. There is also described cDNA derived from human factor IX RNA. Uses include the provision of an intermediate product in the genetic engineering of a factor IX polypeptide precursor and the manufacture of the factor IX polypeptide, and in making products for use in diagnosing the presence of normal or abnormal factor IX in patients with Christmas disease.

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1st amino acid
sequence :

70 75
Glu-Cys-Trp-Cys-Gln-Ala

mRNA : 5' GA^A_G UG^U_C UGG UG^U_C CA^A_G GCN 3'

Deoxyoligonucleotides synthesized : 3' CT^T_C AC^A_G ACC AC^A_G GTT CG (oligo N2A)

3' CT^T_C AC^A_G ACC AC^A_G GTC CG (oligo N2B)

2nd amino acid
sequence :

348 352
His-Met-Phe-Cys-Ala

mRNA : 5' CA^U_C AUG UU^U_C UG^U_C GCN 3'

Deoxyoligonucleotides synthesized : GT^A_G TAC AA^A_G AC^A_G CG (oligo N1)

Fig. 1

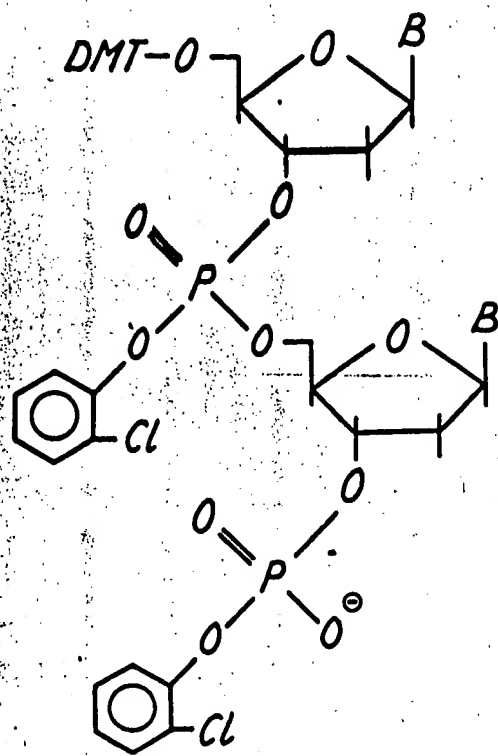


Fig. 2

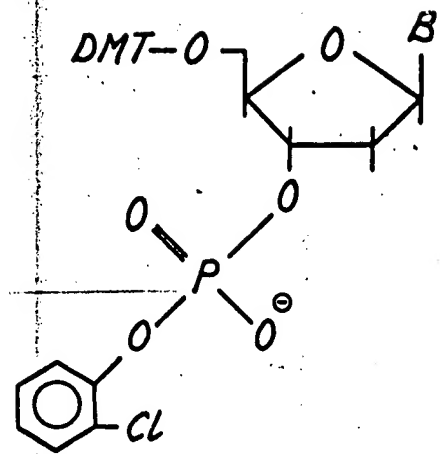


Fig. 3

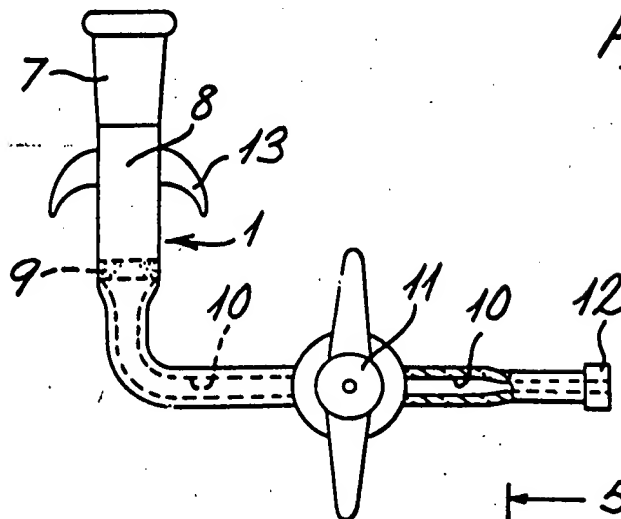
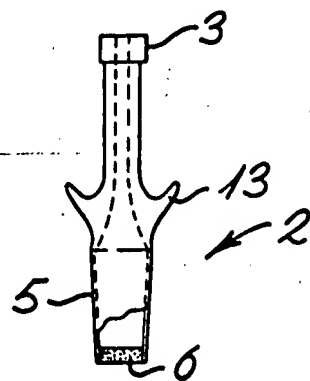


Fig. 4

5cm.

5' TGAATCCAATCCATGTTTAAATGGCGGCATGTGCAAGGATGACATTAATTCCTAT
10 20 30 40 50

70 E C W C Q A G F E G T N C E L D A T C S I K
80
GAATGTTGGTGTCAAGCTGGATTGGAAGGAACGAACTGTGAATTAGATGCAACATGCAGCATTA
60 70 80 90 100 110 120

100 N G C K Q F C K R D T D N K V V C
GAATGGCAGATGCAAGCAGTTTTGTAAAAGGGACACAGATAACAAGGTGGTTTGT
130 140 150 160 170

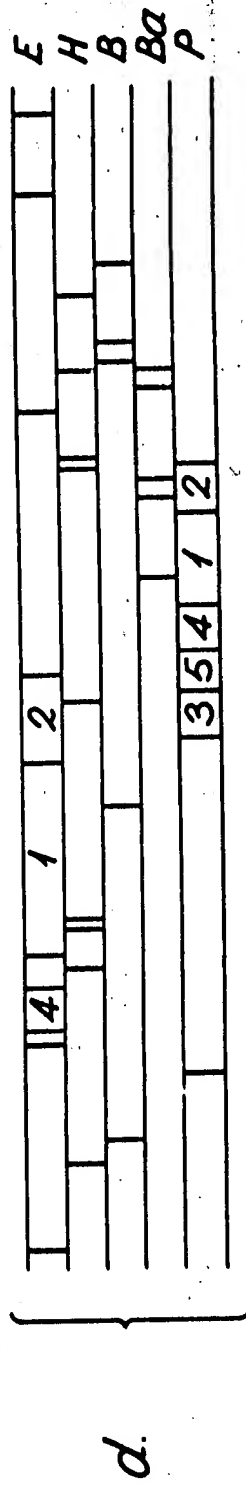
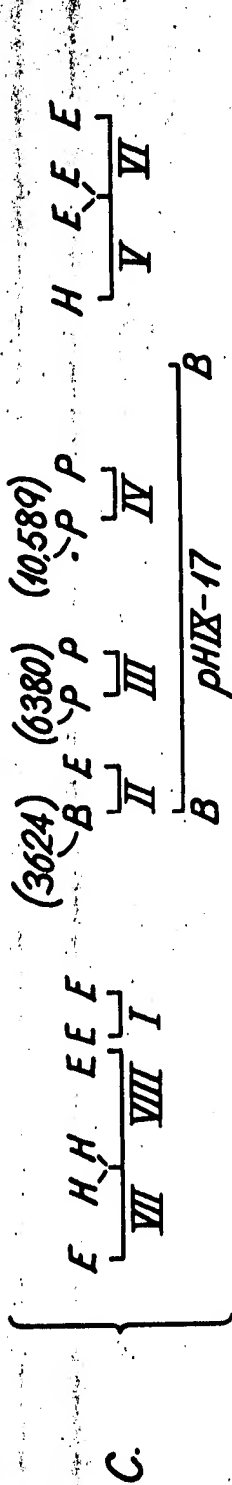
110 S C T D G Y R L A E D Q K S C E P A V P F P
120
TCCTGTACTGACGGATACCGACTTGCAGAAGACCAAAAGTCCTGCGAACCAGCAGTGCCATTTC
180 190 200 210 220 230 240

140 C G R V S V S H V R P R F H G L C S C * E
150
CTGTGGACGAGTCTCTGTCTCACATGTGAGGCCCGCTTTCACGGTCTGTGTTTCGTGCTGAGAA 3'
250 260 270 280 290 300

Fig. 5

a. 5' t u v w x y z 3'

b. 1 Sequenced 11873



1 2 3 4 5 6 7 8 9 10
2010 (10/10/2010)

Fig. 6

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GAATTCCTGTGCCATTATTTATTTCTGGAATCTTCAGCCCTTTAGCTGAAGCAAAAGATTCTGATT...JGAAGCAATATTTCCACCTCTCTGCGCAAAACAGCCAAAGATCAACAG 10 20 30 40 50 60 70 80 90 100 110 120

CAGCAGCAATCTACTGAGCCCTAAAG-GGTGACAAATCTGGAGAAATGATACAGAGGTCTGGTTACTTCTTAGCCCAATGACACAGAAATCACAAATTGAGAAAAACACAGAGTTTATTCATTCC 130 140 150 160 170 180 190 200 210 220 230 240

CATTJTGCCATGCCCTSACAACCAAGCTGCACCTTTTCGTAACTTATCACAACTCTCATATTGACGGAACACTTTCTACAGGTAATGTTTAGTTTGGCTGAACACTTTAGSCAATTGCTTCTG 250 260 270 280 290 300 310 320 330 340 350 360

TAGCAACCAATAATAGCTAGTAACAGAAAGTTCAGGAATATTAACCACTGTAGTGAGSAGAAAGCCCTTTTAATTAATTAATTAATTAATAGAACCAAGTACCATCTTTTGTG-A 370 380 390 400 410 420 430 440 450 460 470 480 490

TCATJCCCTTASTGAATTATTGGTAGCAAGGTTAAAGCTCAAGCTGCTTCTCTCTTGTCCCTG-CAACAGTTGATTT-CCCTCCCTTTATCTCTGAAGTACCGTAAG-ACTAAGAGCCAA 490 500 510 520 530 540 550 560 570 580 590 600

TTATTACATTG-TCATGTCAGCTATATGTAAATAGAGTTTAAAGTTTAGATTTCATCTCACTCAAAATTCATATTCTCCAAACCATACAGTCACTCTGTAGCCTGTGTCTCCCCAG 510 520 530 540 550 560 570 580 590 600 610 620 630 640 650 660 670 680 690 700 710 720

AAAAAGTCACAGCTTATTATTAACTGTGCAATCCCA-GGGGCAAGAGAAAGGAACCTGAAAGTGAGGCAGAAAGGAAAGAAAG-CAATAAGAGGATGAGTTATCAAACTACTCGT 730 740 750 760 770 780 790 800 810 820 830 840

TTCTAACAGCAACGTATTGCTTAATCTCTAGGACTGCTCTCCAATAAGTCAATTG-CCCTCAGGTTAGCCACCTGAGTGGAAGAGCGGTGAAGAATTTGTCTGTCAATCTGTCTC 850 860 870 880 890 900 910 920 930 940 950 960

TCATTGGTTAGAGTTGACATTATGGGAATTAACTC-CTCACATTTCTTAGTTGGATATGCTTGGGTACAGAGGGT-ATAGTACATTACTGCCCTCA-GCATGAACAGGGAAGCTTTCA 970 980 990 1000 1010 1020 1030 1040 1050 1060 1070 1080 1090

FIG. 7a

AGSCAAAGACACATAGTGCAGCTATGASCCCAAGGCAATTCAAGGATACACCCATAGGAGGCTGGTTGACATCCACCCAGAGCTAATCACCACCACCTGCTGGAAAAAGACACAGGTGAAGC
1090 1100 1110 1120 1130 1140 1150 1160 1170 1180 1190 1200

TGAGAAGAATGAAGTGGTGCATAGGAGGTATCTAATACAGTCACCTCATTTTCAAACTTTCCATGTTATGATTGCACCTGACCACCTGAGGATTTCTATTGAAAGTTTTTACTGTGTTGTCAAAC
1210 1220 1230 1240 1250 1260 1270 1280 1290 1300 1310 1320

ACGTACACAAGGGGAAGGTGCTCTTACATTTGTTTATGTTCCCTGTGCTGCTCTAGAAACAGAAA TAGGCTCAAGGCAGAGCCTGTTTTCTTAATTTCAGCAGGCTCTAACTAACAAGTCTCT
1330 1340 1350 1360 1370 1380 1390 1400 1410 1420 1430 1440

GAAACATGCTACTTCTCTGTTATGCTATGATGACAACTTTCAGCTTGGAGTAAAGGAAAGCACAGTAATTAGAAAATACAAAACAAGATGGCAGGAAATAGCCAAAAATATCAGGAACACAAATTTT
1450 1460 1470 1480 1490 1500 1510 1520 1530 1540 1550 1560

GTGAATTGGGATTAAACTAATCTATTATATGACAACTTTTCAGCTTGGAGTTAAAAATTTAATGTTATCTGTTAACGAAAGTGATACCTAAAAATAAAAAATTACACTGGGAGGCCAAAAAT
1570 1580 1590 1600 1610 1620 1630 1640 1650 1660 1670 1680

GAAAGGATGTGAAAAGAACATATCAGGTAAAACCTAACAAAAGAACTAGCAAGCAATCTTAATATCAGACAAAATAGATTCAAGAGGAAAAATCATTTCAAAAAGACAAAGAGATTTTTTT
1690 1700 1710 1720 1730 1740 1750 1760 1770 1780 1790 1800

TATTAATAAGGGGAATTGCATAGGAGAGTAAAGAAATGTGGCCACTGGAAATCTTAGCACTAATGACATATTGGTCTTTGGTCTTCAGTTACCTTACAGGACCCTATTTTCAATTTCTCTT
1810 1820 1830 1840 1850 1860 1870 1880 1890 1900 1910 1920

ATGTTTGATATGTAAACCCTCAGCCAGCTTCAAGTTGCTTTTGGCCCTAATGGACTTCCTAGCACTATAATTTCTTTTTTTTAAATGTTTTTATTTTAGGTTTAGGGGTACATGTGAA
1930 1940 1950 1960 1970 1980 1990 2000 2010 2020 2030 2040

GTTTGTACATAGATATACATGTGTCTCAGGGGTGTGTTGTACATATTATACATGACGCAGATATTTCAGCTCAGTACCAAAATAGTGATCTTTTCTGCTCCCTCCTCATCCACCCCT
2050 2060 2070 2080 2090 2100 2110 2120 2130 2140 2150 2160

2170	2180	2190	2200	2210	2220	2230	2240	2250	2260	2270	2280
2170	2180	2190	2200	2210	2220	2230	2240	2250	2260	2270	2280
2290	2300	2310	2320	2330	2340	2350	2360	2370	2380	2390	2400
2290	2300	2310	2320	2330	2340	2350	2360	2370	2380	2390	2400
2410	2420	2430	2440	2450	2460	2470	2480	2490	2500	2510	2520
2410	2420	2430	2440	2450	2460	2470	2480	2490	2500	2510	2520
2530	2540	2550	2560	2570	2580	2590	2600	2610	2620	2630	2640
2530	2540	2550	2560	2570	2580	2590	2600	2610	2620	2630	2640
2650	2660	2670	2680	2690	2700	2710	2720	2730	2740	2750	2760
2650	2660	2670	2680	2690	2700	2710	2720	2730	2740	2750	2760
2770	2780	2790	2800	2810	2820	2830	2840	2850	2860	2870	2880
2770	2780	2790	2800	2810	2820	2830	2840	2850	2860	2870	2880
2890	2900	2910	2920	2930	2940	2950	2960	2970	2980	2990	3000
2890	2900	2910	2920	2930	2940	2950	2960	2970	2980	2990	3000
3010	3020	3030	3040	3050	3060	3070	3080	3090	3100	3110	3120
3010	3020	3030	3040	3050	3060	3070	3080	3090	3100	3110	3120
3130	3140	3150	3160	3170	3180	3190	3200	3210	3220	3230	3240
3130	3140	3150	3160	3170	3180	3190	3200	3210	3220	3230	3240
3250	3260	3270	3280	3290	3300	3310	3320	3330	3340	3350	3360
3250	3260	3270	3280	3290	3300	3310	3320	3330	3340	3350	3360

FIG. 7c

AATTTATATTTCATAAATTGTCAGAAAGGCAAAATTTCTTTAAATATCAAAAAGTGATCACCATAAAGGAAAAGATTGATAAACTGGACTATATTTAAACTAAGGACTCCTGTTTCAGCAAAAG
3370 3380 3390 3400 3410 3420 3430 3440 3450 3460 3470 3480 3490
ACACTACTTCGACTGAAAGACAACTCACAGAGTGAGACAAAGATATCTGCAATACAGATACCTAATACTGAACCCCATACAGTGATGGGGAATTTAAGTTTCGTACAAATCATTTTAGA
3490 3500 3510 3520 3530 3540 3550 3560 3570 3580 3590 3600
AAATTGCTTGGCAGTAACTCTCTAGATCTGAAACATGTGATCCAGTAATTACACTCATAATTAT AAGCLGTAAAAAGGCATGTTTATGTCCACCAAAAGATATATACAAGAATGTTTCATTA
3610 3620 3630 3640 3650 3660 3670 3680 3690 3700 3710 3720
CACTATTATACATAAAGGCCAATAAAGTGGAAACAAACCAATATCCATTAAACAGTAGAATGAA TAAATAAAAGCTGTAATAGTAATAACAGTGGAAATACACAGCAATGTAAATGAAC
3730 3740 3750 3760 3770 3780 3790 3800 3810 3820 3830 3840
ACTGCTGTACATAAACAATGGTTTAATCTCACAGACAAATGTTAAATGAAGACACAGACGAGTACATATTGCGAACTTCTGTTTATAATTCAGAACTGGCAAGAACTGTTTACTGT
3850 3860 3870 3880 3890 3900 3910 3920 3930 3940 3950 3960
GTTAAGTCCAGTAAATGGTAACCTATAAAGGAAAAGGGTGGAAATGATTGGAGGGGGCATCTTCTGGGGTATTGATAATGTGCTATGTATTGGTCAGTTTAGTTGTTTAAACAGGC
3970 3980 3990 4000 4010 4020 4030 4040 4050 4060 4070 4080
TCATTTACTTTTGAAGAACTTACCTAATAATTTGTGTGTTATTTTGAATATATGTTATACATTAAATAATAGGGTTTTTAAACCTGTAGTTTCATAATTTTAGTGAAAGTAGAATATCCAAA
4090 4100 4110 4120 4130 4140 4150 4160 4170 4180 4190 4200
CATTTAGTTTAAACCAATCAATATAGTGTCTACCATCATTTTATGSCATTATTGASAAAGTTTATTTTACCTTTCTTTCCACTCTTATTTCAAGGCTCCAAAATTTCTCTCCCCAACGTA
4210 4220 4230 4240 4250 4260 4270 4280 4290 4300 4310 4320
TATTGGGGCAACATGAATGCCCCCAATGTATATTGACCCCATACATGAGTCAGTAGTTCCATGTACTTTTAGAATGCCATGTTAAATGATGCTGTTACTGTCTATTTTGGCTTCTTTTA
4330 4340 4350 4360 4370 4380 4390 4400 4410 4420 4430 4440
V T C H I A N S R C E C F C K N S A D N K V C S C T E G Y R L A E N Q K S C
4450 4460 4470 4480 4490 4500 4510 4520 4530 4540 4550 4560
GATGTAACATGTAACATTAAAGATGSCAGATGCGAGCAGTTTTTGTAAATAATAGTGTCTGATCAACAGGTGTTTGTCTCTACTGAGGGATATCGACTTGCAGAAAACCAGAAAGTCTGT

FIG. 7d

GAACCAAGCAGTCATATCTGAATAAGATTTTTTAAGAAATCTGTATCTGAACCTTCAGCA TTTTAAACAACCTACATAATTTTAAATTCCTACTTGAATCTGCTTCTCTTTTGAAATCA
4570 4580 4590 4600 4610 4620 4630 4640 4650 4660 4670 4680

TAGAAAATATCAGTAGCTTGAATTAGACCAATTAATTTTCTAGATTGCATCATATTTTAAATAAAL ATGTAATCATCTACAACCTGAATTTCTTCTGAGTCCAATTTGTCCAATTTT
4690 4700 4710 4720 4730 4740 4750 4760 4770 4780 4790 4800

TTTCTCTAACATTTATATCACAAAGCAATTAATTTGTGTGATTTCCTGCATATGTATTTCTGAATTCATCAAGTCAAAATCAATGTAGTAATACTATATCATAAAAATATACACAAATAATTGA
4810 4820 4830 4840 4850 4860 4870 4880 4890 4900 4910 4920

GTGATAGGCTTCTAGTATAAGGACGGTAAGTTTGAAGCATGATCTCTAGCTGGCTAGTTTACTCTGAGAAAGTTATTTTTTATTTGGGTCTTAAAGCTGAGTTTACACACACTTGGT
4930 4940 4950 4960 4970 4980 4990 5000 5010 5020 5030 5040

GTCAGAAATGATTCGGGCAATGAACCTGTTTATGTTCTGCTAGGCTGATCAGCACAACTATATGGCTGTGAACAAACAATGTTTCCAGTCAATACCAACCATGCCACCATTTTAAACAGC
5050 5060 5070 5080 5090 5100 5110 5120 5130 5140 5150 5160

TGATTAGTGTATTCAGAACATCTCCACTCCATGTTCTGATGGCTGTTATCTAAAGATGAAAGCAGTAGACACTTTTATTTTTTGAATAATTTAGGCTCTGCAGGGTCAATTTATATTGAT
5170 5180 5190 5200 5210 5220 5230 5240 5250 5260 5270 5280

AAATGAGGGCTTTTTTGAAGCAAACTAGATATAATTTCTTTTGCATTTCTAAAGCCTGATATCTTATTAAATTTGGTACATTAAATTTGTGCACCATTTTCTCTGTAACTGTTTCAGTACCTG
5290 5300 5310 5320 5330 5340 5350 5360 5370 5380 5390 5400

TCTCAGCACTATACCAGGCAGAAAGAAATTAAAGAAAGAACCACTGCTGGATCAGCTTGGTCAGGGAGACCCCTAATCTCTGGCACCTAGAGGAATTTAAAGACACACACAGAAAATATA
5410 5420 5430 5440 5450 5460 5470 5480 5490 5500 5510 5520

GASTATGAAGTGGGAATCAGGGGCTCTCACAGCCTTCAGAGCTGAGAGCCCCGAAACAGAGATTTACCCACATATTTATTGACAGCAAGCCAGTCATAAGATTTACTGAAAGTATTCTCTTA
5530 5540 5550 5560 5570 5580 5590 5600 5610 5620 5630 5640

TGGGAAATAAAGGATGAGTCGGCTAGTTATCTGTCAGCAGCAAGCAATGCTCTTAAGGCACAAATCATTATGCAATTTGCTGTGGTTTAAAGAACACCTTTTAAAGCAGTTTTCGCCCTTGGGT
5650 5660 5670 5680 5690 5700 5710 5720 5730 5740 5750 5760

FIG. 7e

GCATTAGACTCTATAAGCTTTACCAATTTCTTCGCAACACCTATTCTATTTCGTAAGATGATGAATTCCGGAGCCAAATGTTCTTTTCATGAAGGATTTGAAACGTGTCCT

6970 6970 6980 6990 7000 7010 7020 7030 7040 7050 7060 7070 7090
 GAAATAACCAACCTTTAGCTTGAGACTCTATTTCACCTGATTTGGATTTTAAATAC TGATGGCC GCTTCTCAGAAGTGACAAGGATGGCCCTCAATCTCAATTTTTTGTAA T

[illegible]

V E P D V D Y V N S T E A E T I L D N I T Q S F N D F T R V V G G E D A K
 .IGT.TTTTTCCTGATGTGGACTATGTAAATCTACTGAAGCTGAACCATTTTGGATAACATCAC TCAAGCACCCCAATCATTTAATGACTTCAC TCGGGTGTGTGGAGAGATGCCAA
 7210 7220 7230 7240 7250 7260 7270 7280 7290 7300 7310 7320

P	G	C	A	T
ACCGGTCATTTCCCTTGCCAGGTACTT	7390	7380	7370	7360
TTATATACTGATCGTGTC	7350	7340	7330	7320
CAAACTGGAGCTCAGCTGCCAAGACACAGGCCAGGTGGGAGACTGAGGCTATT	7310	7300	7290	7280
TTTTACTAGACAGACCTATT	7270	7260	7250	7240
TTGGGA	7230	7220	7210	7200

[illegible]

TAAGGAAACAGCATAACAGGATTCAGACAGSCA---GSTCAACAACATGAAAGTCTGGAAGAAGGTCGCAGGTACTCAGGTTCAGGGCCTTACAGCTTCAGCCCTTGCAAAACCT

GGTGAGAGTTGGAAAGTCTTTAGGCTAAGAAAAATTCGATTATTTAAAGGGGTAAGAGAAAGGACTCAAGGAGGAAGGATTAAGGCAAGAACTAGGTT-CAGGAACAGGGCATGAGAT
7630 7700 7710 7720 7730 7740 7750 7760 7770 7780 7790 7800

AGAGCCTTGATCTACCACTATAGTCTCTCGT		-----GGAAGTGAACGGAGATTAC	
7810	7820	7830	7840
7850	7860	7870	7880
7910	7900	7920	7930

TAACCGA-ATT TGA-AAC-CCTGG-CAACACG-CGAAACCCACCTCTAATTAAAAAATACA AAATTAGCTAGGTGTGATGACTCCACCTGCTCCAGCTATTCCAGGAGGCTGAG
7910 7940 7950 7960 7970 7980 7990 8000 8010 8020 8030 8040

TGGGAGAATCACCTGAGCCTGSAAGTCGAGGCTGCAGTGAATTGTGATCACACCACCTGCACCTTCAGCCTGAGTGCACAGAGTAAGACCCTATCTCAAAAAACAGAAAAAACAACACTG
8050 8060 8070 8080 8090 8100 8110 8120 8130 8140 8150 8160

SCCAAGGAAATGAACCTGTACAGAGCCCGGGTTCAAAACACCAAAATATGCACCTTGACCTAGTCCTTCCCGGGTCTCTGCAGACATTTCTCCAAGCGTAGTCTGCAAAACAACCT
8170 8180 8190 8200 8210 8220 8230 8240 8250 8260 8270 8280

ACATATGTAGAAATTACCTATGCACATTTTTCATTTTAAACAACCAAG-GCTACATTTGTAGCAAAAATCTGGGTGTAACTTAGCCTACAGCTGAAGCCTAAGAGATTCCGTCTGTGAGAAGA
8290 8300 8310 8320 8330 8340 8350 8360 8370 8380 8390 8400

AATAACCCACCTCTTTGGCCCCCTCCCGAGGAGGAGCCAGGATGCTCTTATATAAAGTTGTCTGT-CAATAGGTAACCACTAGCCACATATG--TTTAAATTTTAAATTAACATACA
8410 8420 8430 8440 8450 8460 8470 8480 8490 8500 8510 8520

ATTAGAGAAATTAAATTCATTC-TCAATTGACCTGCCAAATTTAAGCACATTAACAACACATGTGG-TAGTAACACTACTGTATTGGAGAGTGCAGCGGAGATAGAACACTCTAT
8530 8540 8550 8560 8570 8580 8590 8600 8610 8620 8630 8640

TACAGCAGAAATTCATTTGGTAGCAGTTATATAGTTAGTGTAACT-CCTAGTTGCCACAAGTCATGATTAGTAGTAATTTTCATGGA-----
8650 8660 8670 8680 8690 8700 8710 8720 8730 8740 8750 8760

8770 8780 8790 8800 8810 8820 8830 8840 8850 8860 8870 8880

8890 8900 8910 8920 8930 8940 8950 8960 8970 8980 8990 9000

9010 9020 9030 9040 9050 9060 9070 9080 9090 9100 9110 9120

9130 9140 9150 9160 9170 9180 9190 9200 9210 9220 9230 9240

FIG. 7h

FIG. 7i

FIG. 7j

FIG. 7j

GCTCCTTSAGAACTCGGGAAGGAAAGCAGGGTCTCTGAAGAAAATACTTCAGSAGTAGAAGAGGAAAGCTAGAGGGTTAAATGCCACTACACAGGAACAGAAATGAGTTTTTCTTAGAGTTA 11530 11540 11550 11560 11570 11580 11590 11600 11610 11620 11630 11640

GTATATGTCTASAGGTGTAGTAAACTAAACAAGTCTTTGAATTGSCATACCGCCACGCTAGGGAAAGAAATGAAAACCTTTTGAATATTAGTGAAAAAGGAAACTSCAACGCCCTGTATTACT 11650 11660 11670 11680 11690 11700 11710 11720 11730 11740 11750 11760

AGATAGCTTTTCATCAACGGCTCAAAACCGACAGATTTAAAGAAACCAACCCGCTTTTGGCTTCTAAAGCTTTAAATTTGGTTTGGATCCCATGCCCATGACCCTGCCAGCTG.

11770 11780 11790 11800 11810 11820 11830 11840 11850 11860 11870

FIG. 7k

FIG. 8(a)

→ 1 0.000
 30 0.002
 33 0.003
 46 0.004
 48 0.004
 50 0.004
 89 0.007
 94 0.008
 95 0.008
 112 0.009
 120 0.010
 120 0.010
 123 0.010
 123 0.010
 134 0.011
 148 0.012
 173 0.014
 181 0.016
 204 0.017
 247 0.021
 265 0.022
 266 0.022
 266 0.022
 305 0.026
 376 0.032
 417 0.035
 425 0.036
 426 0.036
 465 0.039
 488 0.041
 517 0.043
 523 0.044

 559 0.047
 578 0.049
 590 0.050
 621 0.052
 652 0.055
 → 732 0.062
 733 0.062
 781 0.066
 788 0.066
 816 0.069

ECOR1
 HINF1
 MB011
 ALU1
 DDE1
 MNL1
 MNL1
 MST1
 MHA1
 MB01
 9BV1
 FNU4H1
 BBV1
 FNU4H1
 DDE1
 HPH1
 MNL1
 DDE1
 HINF1
 SPH1
 ALU1
 BBV1
 FNU4H1
 XMN1
 ALU1
 MNL1
 STU1
 HAE111
 RSA1
 DDE1
 ALU1
 ALU1

 MNL1
 RSA1
 DDE1
 ALU1
 HINF1
 HIND111
 ALU1
 MB011
 MNL1
 MNL1

GAATTC
 GAATC
 TCTTC
 AGCT
 CTGAG
 GAGG
 CCTC
 TGC GCA
 GCGC
 GATC
 GCAGC
 GCAGC
 GCAGC
 GCAGC
 CTGAG
 GGTGA
 GAGG
 CTTAG
 GAATC
 GCATGC
 AGCT
 GCTGC
 GCTGC
 GAACACTTTC
 AGCT
 GAGG
 AGGCCT
 GGCC
 GTAC
 CTTAG
 AGCT
 AGCT

 CCTC
 GTAC
 CTAAG
 AGCT
 GATTC
 AAGCTT
 AGCT
 GAAGA
 GAGG
 GAGG

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FIG. 8(b)

818 0.069
 898 0.076
 898 0.076
 899 0.076
 913 0.077
 929 0.078
 976 0.082
 1027 0.086
 1032 0.087
 1054 0.089
 → 1072 0.090
 1073 0.090
 1099 0.092
 1099 0.092
 1101 0.093
 1138 0.096
 1145 0.096
 1150 0.097
 1161 0.098
 1167 0.098
 1193 0.100
 1198 0.101
 1200 0.101
 1204 0.101
 1226 0.103
 1284 0.108
 1286 0.108
 1323 0.111
 1365 0.115
 1365 0.115
 1370 0.115
 1424 0.120
 1427 0.120
 1449 0.122
 1603 0.135
 1626 0.137
 1663 0.137
 1670 0.141
 1672 0.141
 1685 0.142
 1759 0.148
 1766 0.149
 1841 0.155
 1842 0.155

FOK1
 MNL1
 MST11
 DDE1
 DDE1
 HPH1
 TAQ1
 RSA1
 MNL1
 MNL1
 HIND111
 ALU1
 BBV1
 FNU4H1
 ALU1
 MNL1
 HINC11
 FOK1
 ALU1
 HPH1
 HPH1
 ALU1
 DDE1
 MB011
 MNL1
 DDE1
 MNL1
 RSA1
 BBV1
 FNU4H1
 XBA1
 DDE1
 ALU1
 RSA1
 ALU1
 ACC1
 HINC11
 HPH1
 MNL1
 HAE111
 FOK1
 HINF1
 MNL1
 SAU961
 HAE111

GGATG
 CCTC
 CCTCAGG
 CTCAG
 CTGAG
 GGTGA
 TCGA
 GTAC
 GAGG
 CCTC
 AAGCTT
 AGCT
 GCAGC
 GCAGC
 AGCT
 GAGG
 GTTGAC
 CATCC
 AGCT
 TCACC
 GGTGA
 AGCT
 CTGAG
 GAAGA
 GAGG
 CTGAG
 GAGG
 GTAC
 GCTGC
 GCTGC
 TCTAGA
 CTAAG
 AGCT
 GTAC
 AGCT
 GTATAC
 GGTAAAC
 GTTAAAC
 GAGG
 GGCC
 GGATG
 GATTC
 GAGG
 GGGCC
 GGCC

FIG. 8(c)

1855 0.156
1884 0.159
1901 0.160
1901 0.160
1939 0.163
1940 0.163

DDE1
MBO11
AVA11
SAU961
MNL1
DDE1

CTTAG
TCTTC
GGACC
GGACC
CCTC
CTCAG

1947 0.164
1965 0.165
1965 0.165
2030 0.171
2081 0.175
2097 0.177
2110 0.178
2112 0.178
2116 0.178
2128 0.179
2141 0.180
2147 0.181
2150 0.181
2158 0.182
2161 0.182
2165 0.182
2171 0.183
2174 0.183
2222 0.187
2225 0.187
2248 0.189
2282 0.192
2283 0.192
2287 0.193
2296 0.193
2301 0.194
2349 0.198
2349 0.198
2422 0.204
2468 0.208
2483 0.209
2503 0.211
2524 0.212
2534 0.213

ALU1
HAE111
SAU961
RSA1
RSA1
HGA1
ALU1
DDE1
RSA1
MBO1
MNL1
MNL1
FOK1
MNL1
MNL1
MNL1
MNL1
ACC1
HINF1
DDE1
ALU1
PST1
MST11
DDE1
FOK1
MNL1
ALU1
BBV1
FNU4H1
HINF1
HINF1
BSTE11
ALU1
XBA1
DDE1

AGCT
GGCC
GGCCC
GTAC
GTAC
GACGC
AGCT
CTCAG
GTAC
GATC
CCTC
CCTC
CATCC
CCTC
CCTC
CCTC
GTAGAC
GACTC
CTTAG
AGCT
CTGCAG
CCTAAGG
CTAAG
GGATG
CCTC
AGCT
GCTGC
GCTGC
GATTC
GATTC
GGTAACC
AGCT
TCTAGA
CTAAG

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FIG. 8(d)

2658 0.224
2678 0.225
2726 0.230
2728 0.230
2770 0.233
2807 0.236
2811 0.237
2965 0.250
2984 0.251
2984 0.251
3012 0.254
3024 0.255
3032 0.255
3048 0.257
3090 0.260
3093 0.260
306 0.262
3141 0.264
3168 0.267
3193 0.269
3213 0.271
3216 0.271
3220 0.271
3234 0.272
3263 0.275
3333 0.281
3412 0.287

RSA1
SFNA1
HINF1
HINC11
HINF1
HGA1
DDE1
HINF1
AVA11
SAU961
MNL1
HINF1
ALU1
NDE1
MNL1
MB011
RSA1
TAQ1
RSA1
MB01
HGIA1
DDE1
MB011
RSA1
MNL1
NDE1
BCL1

GTAC
GCATC
GAGTC
GTCAAC
GATTC
GACGC
CTTAG
GATTC
GGTCC
GGTCC
GAGG
GATTC
AGCT
CATATG
GAGG
GAAGA
GTAC
TCGA
GTAC
GATC
GTGCTC
CTCAG
GAAGA
GTAC
GAGG
CATATG
TGATCA

3413 0.287
3415 0.288
3457 0.291
3462 0.292
3489 0.294
3522 0.297
3585 0.302
→ 3624 0.305
3625 0.305
3638 0.306
3689 0.311
3792 0.319

MB01
HPH1
DDE1
HINF1
TAQ1
ECOR5
RSA1
BGL11
MB01
MB01
HPH1
ALU1

GATC
TCACC
CTAAG
GACTC
TCGA
GATATC
GTAC
AGATCT
GATC
GATC
TCACC
AGCT

FIG. 8(e)

3847	0.324	RSA1	GTAC
3905	0.329	RSA1	GTAC
3970	0.334	BSTN1	CCAGG
3970	0.334	SCRF1	CCAGG
3979	0.335	BSTE11	GGTAACC
4016	0.338	MNL1	GAGG
4022	0.339	SFNA1	GCATC
4025	0.339	MBO11	TCTTC
4368	0.368	HINF1	GAGTC
4384	0.369	RSA1	GTAC
4410	0.371	SFNA1	GATGC
4469	0.376	SFNA1	GATGC
4520	0.381	RSA1	GTAC
4523	0.381	DDE1	CTGAG
4525	0.381	MNL1	GAGG
4529	0.381	ECORS	GATATC
4533	0.382	TAQ1	TCGA
4658	0.392	HINF1	GAATC
4695	0.395	ALU1	AGCT
4719	0.397	XBA1	TCTAGA
4727	0.398	SFNA1	GCATC
→ 4769	0.402	ECOR1	GAATTC
4769	0.402	XMN1	GAATTCCTTC
4778	0.402	DDE1	CTGAG
4780	0.403	HINF1	GAGTC
4848	0.408	NDE1	CATATG
4961	0.418	HINF1	GATTC
4988	0.420	DDE1	CTGAG
5020	0.423	ALU1	AGCT
5022	0.423	DDE1	CTGAG
5049	0.425	HINF1	GATTC
5053	0.426	HPA11	CCGG
5085	0.428	BCL1	TGATCA
5086	0.428	MBO1	GATC
→ 5157	0.434	PVU11	CAGCTG
5158	0.434	ALU1	AGCT
5225	0.440	ACC1	GATGAC
5258	0.443	PST1	CTGCAG
5285	0.445	MNL1	GAGG
5339	0.450	ECORS	GATATC
5355	0.451	RSA1	GTAC
5367	0.452	HGIA1	GTGCAC
5394	0.454	RSA1	GTAC
5402	0.455	DDE1	CTCAG
5414	0.456	BSTN1	CCAGG

FIG. 8(f)

5414 0.456
5421 0.456
5451 0.459
5455 0.459

SCRF1
MB011
MB01
ALU1

CCAGG
GAAGA
GATC
AGCT

5481 0.462
5490 0.462
5560 0.468
5562 0.468
5627 0.474
5653 0.476
5657 0.476
5672 0.478
5674 0.478
5674 0.478
5754 0.485
5754 0.485
5761 0.485
5762 0.485
5764 0.485
5764 0.485
5779 0.487
5813 0.490
5821 0.490
5844 0.492
5844 0.492
5845 0.492
5863 0.494
5864 0.494
5875 0.495
5876 0.495
5886 0.496
5887 0.496
5898 0.497
5899 0.497
5900 0.497
5922 0.499
5952 0.501
5955 0.501
5961 0.502
5971 0.503

FNU4H1
MNL1
ALU1
DDE1
XMN1
FOK1
HINF1
PST1
BBV1
FNU4H1
BSTN1
SCRF1
SAU961
HAE111
BSTN1
SCRF1
MNL1
ECOR5
HAE111
BBV1
FNU4H1
PST1
BAL1
HAE111
SAU961
HAE111
BAL1
HAE111
MNL1
STU1
HAE111
ALU1
MB011
HINF1
DDE1
SAU961

GGGGC
GAGC
AGCT
CTGAG
GAAAGTATTC
GGATG
GAGTC
CTGCAG
GCAGC
GCAGC
CCTGG
CCTGG
GGGCC
GGCC
CCAGG
CCAGG
CCTC
GATATC
GGCC
GCTGC
GCTGC
CTGCAG
TGGCCA
GGCC
GGGCC
GGCC
TGGCCA
GGCC
GAGG
AGGCCT
GGCC
AGCT
GAAGA
GAATC
CTAAG
GGGCC

FIG. 8(g)

5972	0.503	HAE111	GGCC
5987	0.504	MB011	TCTTC
5994	0.505	BSTN1	CCTGG
5994	0.505	SCRF1	CCTGG
6000	0.505	MB011	TCTTC
6021	0.507	ALU1	AGCT
6026	0.507	ACC1	GTCTAC
6037	0.508	MNL1	GAGG
6121	0.515	ALU1	AGCT
6139	0.517	MB011	TCTTC
6177	0.520	MNL1	CCTC
6211	0.523	DDE1	CTTAG
6214	0.523	ALU1	AGCT
6233	0.525	HAE111	GGCC
→ 6248	0.526	HIND111	AAGCTT
6249	0.526	ALU1	AGCT
6275	0.528	AVA11	GGTCC
6275	0.528	SAU961	GGTCC
6305	0.531	RSA1	GTAC
6361	0.536	MB011	TCTTC
6370	0.537	BBV1	GCAGC
6379	0.537	FNU4H1	GCAGC
→ 6380	0.537	PVU11	CAGCTG
6381	0.537	ALU1	AGCT
6558	0.552	AVA11	GGTCC
6558	0.552	SAU961	GGTCC
6561	0.553	BSTN1	CCTGG
6561	0.553	SCRF1	CCTGG
6564	0.553	HPH1	GGTGA
6629	0.558	HINF1	GAATC
6639	0.559	MB01	GATC
6674	0.562	HINF1	GAATC
6677	0.562	XBA1	TCTAGA
6683	0.563	STU1	AGGCCT
6684	0.563	HAE111	GGCC
6722	0.566	BBV1	GCAGC
6722	0.566	FNU4H1	GCAGC
6767	0.570	SFNA1	GCATC
6793	0.572	FOK1	GGATG
6848	0.577	HINF1	GACTC

FIG. 8(h)

6874 0.579
6911 0.582
6916 0.582
6984 0.588
6991 0.589
7028 0.592
7029 0.592
7038 0.593
7052 0.594
7056 0.594
7057 0.594
7059 0.594
7124 0.600
7155 0.603
7155 0.603
7179 0.605
7182 0.605
7185 0.605
7194 0.606
7196 0.606
7237 0.609
7293 0.614
7310 0.616
7313 0.616
7322 0.617
7322 0.617
7343 0.618
7373 0.621
7373 0.621
7374 0.621
7376 0.621
→ 7378 0.621
7379 0.621
7394 0.623
7396 0.623
7396 0.623
7408 0.624
7410 0.624
7438 0.626
7485 0.630
7486 0.630
7488 0.631
7507 0.632
7516 0.633
7529 0.634
7547 0.636

HINF1
ECOR1
HPA11
ALU1
HINF1
SAU961
HAE111
DDE1
FOK1
SAU961
HAE111
MNL1
MB011
MB011
XMN1
DDE1
ALU1
HPI1
DDE1
MNL1
ALU1
AVA1
MB011
SFNA1
BSTN1
SCRF1
RSA1
HGIA1
SAC1
ALU1
DDE1
PVU11
ALU1
HAE111
BSTN1
SCRF1
DDE1
MNL1
FOK1
STU1
HAE111
MNL1
HPI1
MNL1
ALU1
MRO11

GATTC
GAATTC
CCGG
AGCT
GACTC
GGGCC
GGCC
CTCAG
GGATG
GGGCC
GGCC
CCTC
TCTTC
GAAGA
GAAGAGTTTC
CTAAG
AGCT
TCACC
CTGAG
GAGG
AGCT
CTCGGG
GAAGA
GATGC
CCAGG
CCAGG
GTAC
GAGCTC
GAGCTC
AGCT
CTCAG
CAGCTG
AGCT
GGCC
CCAGG
CCAGG
CTGAG
GAGG
GGATG
AGGCCT
GGCC
CCTC
GGTGA
GAGG
AGCT
GAAGA

FIG. 8(i)

7580	0.638	HINF1	GATTC
7599	0.640	HINC11	GTCAAC
7619	0.642	MB011	GAAGA
7634	0.643	RSA1	GTAC
7637	0.643	DDE1	CTCAG
7659	0.645	ALU1	AGCT
7681	0.647	HPH1	GGTGA
7705	0.649	DDE1	CTAAG
7745	0.652	HINF1	GACTC
7753	0.653	MNL1	GAGG
7802	0.657	HINF1	GAGTC
7809	0.658	MB01	GATC
7940	0.669	BSTN1	CCTGG
7940	0.669	SCR11	CCTGG
7963	0.671	MNL1	CCTC
7989	0.673	ALU1	AGCT
8002	0.674	HINF1	GACTC
8013	0.675	HGIA1	GTGCTC
8021	0.675	ALU1	AGCT
8031	0.676	MNL1	GAGG
8035	0.677	DDE1	CTGAG
8037	0.677	MNL1	GAGG
8046	0.678	HINF1	GAATC
8049	0.678	HPH1	TCACC
8053	0.678	DDE1	CTGAG
8058	0.679	BSTN1	CCTGG
8058	0.679	SCR11	CCTGG
8067	0.679	TAQ1	TCGA
8069	0.680	MNL1	GAGG
8072	0.680	BBV1	GCTGC
8072	0.680	FNU4H1	GCTGC
8073	0.680	PST1	CTGCAG
8086	0.681	BCL1	TGATCA
8087	0.681	MB01	GATC
8109	0.683	DDE1	CTGAG
8160	0.687	HAE111	GGCC
8160	0.687	SAU961	GGCCC
8190	0.690	HPA11	CCGG

FIG. 8(j)

8190 0.690
8190 0.690
8220 0.692
8233 0.693
8233 0.693
8233 0.693
8233 0.693
8234 0.693
8234 0.693
8234 0.693
8238 0.694
8243 0.694
8282 0.697
8357 0.704
8366 0.705
8367 0.705
8376 0.705
8382 0.706
8396 0.707
8410 0.708
8417 0.709
8417 0.709
8423 0.709

NCI1
SCRF1
RSA1
AVA1
NCI1
SCRF1
SMA1
HPA11
NCI1
SCRF1
HGIA1
PST1
NDE1
DDE1
PVU11
ALU1
DDE1
HINF1
MB011
MNL1
HAE111
SAU961
MNL1

CCGGG
CCGGG
GTAC
CCCGGG
CCCGG
CCCGG
CCCGGG
CCGG
CCGGG
CCGGG
GTGCTC
CTGCAG
CATATG
CTTAG
CAGCTG
AGCT
CTAAG
GATTC
GAAGA
CCTC
GGCC
GGCCC
CCTC

8428 0.710
8428 0.710
8440 0.711
8440 0.711
8443 0.711
8447 0.711
8447 0.711
8477 0.714
8492 0.715
8643 0.728
9221 0.777
9263 0.780
9266 0.780
9294 0.783
9335 0.786
9350 0.787

BSTN1
SCRF1
BSTN1
SCRF1
FOK1
AVA11
SAU961
BSTE11
NDE1
PST1
MB01
MNL1
MNL1
MNL1
FOK1
MB011

CCAGG
CCAGG
CCAGG
CCAGG
GGATG
GGTCC
GGTCC
GGTAACC
CATATG
CTGCAG
GATC
CCTC
CCTC
GAGG
CATCC
TCTTC

FIG. 8(k)

9353	0.788	MB011	TCTTC
9394	0.791	BSTN1	CCTGG
9394	0.791	SCRF1	CCTGG
9406	0.792	MNL1	CCTC
9550	0.804	MB01	GATC
9571	0.806	MB011	TCTTC
9600	0.808	HGIA1	GTGCTC
9603	0.809	DDE1	CTCAG
→ 9614	0.810	SAMH1	GGATCC
9615	0.810	MB01	GATC
9626	0.811	BSTN1	CCAGG
9626	0.811	SCRF1	CCAGG
9641	0.812	ALU1	AGCT
9643	0.812	DDE1	CTAAG
9647	0.812	MB011	GAAGA
9676	0.815	HINF1	GATTC
968	0.816	MB01	GATC
9694	0.816	FOK1	CATCC
9697	0.817	BSTN1	CCTGG
9697	0.817	SCRF1	CCTGG
9723	0.819	MB011	TCTTC
9747	0.821	NCI1	CCCGG
9747	0.821	SCRF1	CCCGG
9748	0.821	HPA11	CCGG
9762	0.822	HAE11	GGCGCC
9762	0.822	NAR1	GGCGCC
9763	0.822	HHA1	GC GC
9777	0.823	ALU1	AGCT
9787	0.824	MNL1	GAGG
9791	0.825	DDE1	CTGAG
9793	0.825	MNL1	GAGG
9814	0.826	HPA11	CCGG
9814	0.826	NCI1	CCGGG
9814	0.826	SCRF1	CCGGG
9819	0.827	MNL1	GAGG
9826	0.828	ALU1	AGCT
9843	0.829	MB01	GATC
9864	0.831	BSTN1	CCTGG
9864	0.831	SCRF1	CCTGG
9881	0.832	HINF1	GACTC
10246	0.863	HINF1	GATTC
10279	0.866	ALU1	AGCT
10281	0.866	DDE1	CTGAG
10284	0.866	ALU1	AGCT
10310	0.868	TTM1111	GACCC TGT C

FIG. 8(L)

10336 0.870
10347 0.871
10351 0.872
10455 0.880
10463 0.881
10473 0.882
10477 0.882
10478 0.882
10482 0.883
10505 0.885
10512 0.885
10536 0.887
10543 0.888
10545 0.888
10545 J.888
10563 0.890
10568 0.890
10589 0.892
10590 0.892
10605 0.893
10625 0.895
10656 0.897
10685 0.900
10692 0.901
10733 0.904
10733 0.904
10751 0.905
10752 0.905
10760 0.906
10763 0.906
10779 0.908
10865 0.915
10869 0.915
10899 0.918
10925 0.920
10950 0.922
10958 0.923
11015 0.928

MNL1
MNL1
FOK1
HINF1
MNL1
FOK1
SAU961
HAE111
ALU1
PST1
MNL1
M301
PST1
B3V1
FNU4H1
DDE1
SFNA1
PVU11
ALU1
HPH1
ALU1
HPH1
SFNA1
M3011
BSTN1
SCRF1
ECL1
ME01
HPH1
MB011
MB011
HPH1
ALU1
MB011
HPH1
HINF1
MNL1
B3V1

CCTC
CCTC
CATCC
GAATC
CCTC
GGATG
GGGCC
GGCC
AGCT
CTGCAG
GAGG
GATC
CTGCAG
GCAGC
GCAGC
CTAAG
GCATC
CAGCTG
AGCT
GGTGA
AGCT
TCACC
GATGC
TCTTC
CCAGG
CCAGG
TGATCA
GATC
GGTGA
GAAGA
GAAGA
GGTGA
AGCT
GAAGA
GGTGA
GATTC
CCTC
GCAGC

FIG. 8(m)

11015	0.928	FNU4H1	GCAGC
11061	0.932	HINC11	GTTGAC
11073	0.933	ALU1	AGCT
11095	0.934	FNU4H1	GCGGC
11132	0.938	HPH1	TCACC
11135	0.938	BSTN1	CCTGG
11135	0.938	SCRF1	CCTGG
11137	0.938	BAL1	TGGCCA
11138	0.938	HAE111	GGCC
11145	0.939	MB01	GATC
11157	0.940	DDE1	CTAAG
11170	0.941	BAMH1	GGATCC
11171	0.941	MB01	GATC
11181	0.942	ALU1	AGCT
11256	0.948	BSTN1	CCAGG
11256	0.948	SCRF1	CCAGG
11265	0.949	HPH1	TCACC
11268	0.949	MNL1	CCTC
11268	0.949	DDE1	CTCAG
11272	0.949	ALU1	AGCT
11278	0.950	BSTN1	CCAGG
11278	0.950	SCRF1	CCAGG
11300	0.952	BBV1	GCAGC
11300	0.952	FNU4H1	GCAGC
11303	0.952	FNU4H1	GCCGC
11314	0.953	NRU1	TCGCGA
11315	0.953	FNUD11	CGCG
11324	0.954	ALU1	AGCT
11330	0.954	BSTN1	CCAGG
11330	0.954	SCRF1	CCAGG
11349	0.956	HPA11	CCGG
11356	0.956	HAE11	GGCGCT
11357	0.956	HHA1	GCGC
11367	0.957	FOK1	CATCC
11381	0.958	MNL1	CCTC
11428	0.962	FNUD11	CGCG
11429	0.963	HHA1	GCGC
11447	0.964	HPA11	CCGG
11464	0.965	MNL1	GAGG

FIG. 8(n)

11466	0.966	HAE111	GGCC
11478	0.967	MNL1	GAGG
11481	0.967	RSA1	GTAC
11494	0.968	MNL1	CCTC
11497	0.968	BSTN1	CCAGG
11497	0.968	SCRF1	CCAGG
11500	0.968	HAE111	GGCC
11500	0.968	SAU961	GGCCC
11504	0.969	FNUD11	CGCG
11505	0.969	HHA1	GCGC
11506	0.969	FNUD11	CGCG
11515	0.970	DDE1	CTCAG
11519	0.970	HGIA1	GAGCTC
11519	0.970	SAC1	GAGCTC
11520	0.970	ALU1	AGCT
11533	0.971	AVA1	CTCGGG
11557	0.973	MB011	GAAGA
11560	0.974	XMN1	GAAATACTTC
11581	0.975	MNL1	GAGG
11586	0.976	ALU1	AGCT
11591	0.976	MNL1	GAGG
11631	0.980	DDE1	CTTAG
11648	0.981	XBA1	TCTAGA
11652	0.981	MNL1	GAGG
11701	0.985	MB011	GAAGA
11765	0.991	ALU1	AGCT
11778	0.992	ALU1	AGCT
→ 11828	0.996	HIND111	AAGCTT
11829	0.996	ALU1	AGCT
11845	0.998	BAMH1	GGATCC
11846	0.998	MB01	GATC
→ 11868	0.999	PVU11	CAGCTG
11869	1.000	ALU1	AGCT

M I W A E S P G L I Y I C L L G Y L L S A E C T V F L D M E N A M K
 TTTTCTAGCAGATTG TGAACATGATCATGGCAGAA* CACCAGGCCTCATCACCATCTGCCTTTTAGGATATCTACTCAGTCTGCTGAATGTACAGTTTTTCTTGTGATCATGAAAACGCCAACCA
 10 20 30 40 50 60 70 80 90 100 110 120

	I	L	N	K	F	Y	N	S	G	K	L	E	E	F	V	J	G	N	L	E	R	E	C	M	E	E	K	C	S	F	E	E	A	R	E	V	F	E				
104	AA	AT	TC	GA	TC	CG	CC	AA	AA	AG	GT	AT	AT	TC	AG	GT	AT	AT	TC	AG	GT	AT	AT	TC	AG	GT	AT	AT	TC	AG	GT	AT	AT	TC	AG	GT	AT	AT	TC	AG	GT	AT
105	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320	330	340	350	360	370	380	390	400	410	420	430	440	450	460	470	480	490	500	510	520		

	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360	380	400																						
N	T	E	E	T	T	E	F	M	K	C	Y	V	E	G	D	L	C	E	S	N	P	C	L	N	G	G	S	C	K	D	D	I	N	S	Y	E	C	W			
AA	AC	CT	EA	AA	CA	CA	CT	GA	AT	TT	GG	AG	CAG	AT	GT	GT	CT	GG	AG	AT	CC	AT	GT	TA	AT	GG	CG	CG	AG	GT	CA	AT	TA	TT	CT	AT	CA	AT	GT	TT	GT
250	250	250	250	250	250	250	250	270	270	290	290	290	290	290	290	300	300	300	300	310	310	310	320	320	320	320	330	330	330	340	340	340	350	350	360	360	360	360	360	360	

[illegible]

	120	140
G Y R L A E N Q K S C E P A V P F P C G F V S V S C T S K L T R A E A V F P O V		
AGGGATTCGACTTGCAGAAACCAAGTCCTGTGAACCCAGCAGTCCCATTTCCATGTGGACAGTTCTCTGTTTCACAACTTCTAAGCTCACCCGTCGAGGCTGTTTTTCCCTGATG	450	590
	500	600
	510	580
	520	570
	530	560
	540	550

160
 ← W I X →
 180
 L Y V W S T E A E T I L D N I T L S T Q S F N D F T R V G C E D A K P G C F P
 TGGACTTGTCTAAATTTCTACTGTPASCTGAACCATTTTGGATAACATCTCAAGCACCCCAATCATTTTAATGACTTCACCTCGGGTGTGGTGGAGAGATGCCAAACAGGTCAATTC
 610 620 630 640 650 660 670 680 690 700 710 720

	200	220
W Q V V L M G K V D A F C G S I V K E K W I V T A A H C V E T G V K I T V V :		
CTTGGCAGCTTTTGAATGCTAAAGTTTGATGCACTCTGTCGGAGCGCTCTATCGTTAACTGAAATGAAAATGGATTGTAACCTGCTGCCCACTGTTGAAACCTGGTGTTAAATAATACAGTTGTGG	746	830
	750	820
	760	810
	770	800
	780	
	790	

240
 260
 C E P M I E E T E H T E J K R N V I R I I P H N Y N A A I N K Y N M D I A L L
 C A C T C G A C A T A T T G A G G A C A G A C A C A T A C A C C A A A A G C G A A T G I G A T T C G A A T T A T T C C T C A C C A C A C T A C A A T G C A G C T A T T A A T A A G T A C A A C C A T G A C A J T T G C C C T T C
 86C 870 890 890 900 910 92J 930 940 950 960

280 → 300
 E L D E F L V L N S V V T P I C I A D K E Y T N I F L K F G S G V V S G W G R V
 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 2100 2200 2300 2400 2500 2600 2700 2800 2900 3000 3100 3200 3300 3400 3500 3600 3700 3800 3900 4000 4100 4200 4300 4400 4500 4600 4700 4800 4900 5000 5100 5200 5300 5400 5500 5600 5700 5800 5900 6000 6100 6200 6300 6400 6500 6600 6700 6800 6900 7000 7100 7200 7300 7400 7500 7600 7700 7800 7900 8000 8100 8200 8300 8400 8500 8600 8700 8800 8900 9000 9100 9200 9300 9400 9500 9600 9700 9800 9900 10000 10100 10200 10300 10400 10500 10600 10700 10800 10900 11000 11100 11200 11300 11400 11500 11600 11700 11800 11900 12000 12100 12200 12300 12400 12500 12600 12700 12800 12900 13000 13100 13200 13300 13400 13500 13600 13700 13800 13900 14000 14100 14200 14300 14400 14500 14600 14700 14800 14900 15000 15100 15200 15300 15400 15500 15600 15700 15800 15900 16000 16100 16200 16300 16400 16500 16600 16700 16800 16900 17000 17100 17200 17300 17400 17500 17600 17700 17800 17900 18000 18100 18200 18300 18400 18500 18600 18700 18800 18900 19000 19100 19200 19300 19400 19500 19600 19700 19800 19900 20000 20100 20200 20300 20400 20500 20600 20700 20800 20900 21000 21100 21200 21300 21400 21500 21600 21700 21800 21900 22000 22100 22200 22300 22400 22500 22600 22700 22800 22900 23000 23100 23200 23300 23400 23500 23600 23700 23800 23900 24000 24100 24200 24300 24400 24500 24600 24700 24800 24900 25000 25100 25200 25300 25400 25500 25600 25700 25800 25900 26000 26100 26200 26300 26400 26500 26600 26700 26800 26900 27000 27100 27200 27300 27400 27500 27600 27700 27800 27900 28000 28100 28200 28300 28400 28500 28600 28700 28800 28900 29000 29100 29200 29300 29400 29500 29600 29700 29800 29900 30000 30100 30200 30300 30400 30500 30600 30700 30800 30900 31000 31100 31200 31300 31400 31500 31600 31700 31800 31900 32000 32100 32200 32300 32400 32500 32600 32700 32800 32900 33000 33100 33200 33300 33400 33500 33600 33700 33800 33900 34000 34100 34200 34300 34400 34500 34600 34700 34800 34900 35000 35100 35200 35300 35400 35500 35600 35700 35800 35900 36000 36100 36200 36300 36400 36500 36600 36700 36800 36900 37000 37100 37200 37300 37400 37500 37600 37700 37800 37900 38000 38100 38200 38300 38400 38500 38600 38700 38800 38900 39000 39100 39200 39300 39400 39500 39600 39700 39800 39900 40000 40100 40200 40300 40400 40500 40600 40700 40800 40900 41000 41100 41200 41300 41400 41500 41600 41700 41800 41900 42000 42100 42200 42300 42400 42500 42600 42700 42800 42900 43000 43100 43200 43300 43400 43500 43600 43700 43800 43900 44000 44100 44200 44300 44400 44500 44600 44700 44800 44900 45000 45100 45200 45300 45400 45500 45600 45700 45800 45900 46000 46100 46200 46300 46400 46500 46600 46700 46800 46900 47000 47100 47200 47300 47400 47500 47600 47700 47800 47900 48000 48100 48200 48300 48400 48500 48600 48700 48800 48900 49000 49100 49200 49300 49400 49500 49600 49700 49800 49900 50000 50100 50200 50300 50400 50500 50600 50700 50800 50900 51000 51100 51200 51300 51400 51500 51600 51700 51800 51900 52000 52100 52200 52300 52400 52500 52600 52700 52800 52900 53000 53100 53200 53300 53400 53500 53600 53700 53800 53900 54000 54100 54200 54300 54400 54500 54600 54700 54800 54900 55000 55100 55200 55300 55400 55500 55600 55700 55800 55900 56000 56100 56200 56300 56400 56500 56600 56700 56800 56900 57000 57100 57200 57300 57400 57500 57600 57700 57800 57900 58000 58100 58200 58300 58400 58500 58600 58700 58800 58900 59000 59100 59200 59300 59400 59500 59600 59700 59800 59900 60000 60100 60200 60300 60400 60500 60600 60700 60800 60900 61000 61100 61200 61300 61400 61500 61600 61700 61800 61900 62000 62100 62200 62300 62400 62500 62600 62700 62800 62900 63000 63100 63200 63300 63400 63500 63600 63700 63800 63900 64000 64100 64200 64300 64400 64500 64600 64700 64800 64900 65000 65100 65200 65300 65400 65500 65600 65700 65800 65900 66000 66100 66200 66300 66400 66500 66600 66700 66800 66900 67000 67100 67200 67300 67400 67500 67600 67700 67800 67900 68000 68100 68200 68300 68400 68500 68600 68700 68800 68900 69000 69

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FIG. 9(b)

320
F M K S G L V L S Y L R V P L V D R A C L R S T K F T I Y N M F C A G F
1050 1100 1110 1120 1130 1140 1150 1160 1170 1180 1190 1200
1010 1020 1030 1040 1050 1060 1070 1080 1090 1100 1110 1120
340
M E S G H D S L S G D S G G P H V T E V E G T S F L T G I I S W G E E C A P K
1210 1220 1230 1240 1250 1260 1270 1280 1290 1300 1310 1320
1230 1240 1250 1260 1270 1280 1290 1300 1310 1320 1330 1340
415
K Y G I V T V S S Y V N W I K E K T K L T *
1350 1360 1370 1380 1390 1400 1410 1420 1430 1440 1450 1460
1370 1380 1390 1400 1410 1420 1430 1440 1450 1460 1470 1480
380
G C C I C A C T A A C T A C T C C C A T C T T T T G T T G A T T T G A T A T A T A C A T T C T A T G A T C A T T T C T C T T T T C T C T T T T C A G G G A G A A T T C A T A T T T T A C C T G A G C A A T T G A T T A G
1490 1500 1510 1520 1530 1540 1550 1560 1570 1580 1590 1600
1510 1520 1530 1540 1550 1560 1570 1580 1590 1600 1610 1620
AAA T G G A A C C A C T A G A G G A T A T A A T S T G T T A G G A A T T A C A G T C A T T T C T A A G G G C C C A G C C T T G A C A A A T T G T G A A T T C C A C T C T G T C C A T C A G A T A C T A T G G T C T
1630 1640 1650 1660 1670 1680 1690 1700 1710 1720 1730 1740
1650 1660 1670 1680 1690 1700 1710 1720 1730 1740 1750 1760
C C A C T A T G C C A A C T A C T C A T T T T C C C C T T T T T G C C T T C C A C C A A A C A C A T C A A T G T T A T T A G T T C T G T A T A C A G T A C A G G A T C T
1770 1780 1790 1800 1810 1820 1830 1840 1850 1860 1870 1880
1790 1800 1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
T T G G T A C T C T A T C A C A G C C A G T A C C A C A C T C A T C A G A G A A G A C A C A G G A G T A G T C T C C C T T T A C C T C C A T C A T C A A A A C A C T A C T C T T T C C C T A C C C T A T T C C T C A A T C T T T
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020
1930 1940 1950 1960 1970 1980 1990 2000 2010 2020 2030 2040
T A C C T T T T C A A T C C A A T C C C A A T C A G T T T T C T C T T T C T T A C T C C C T C T C C C T T T A C C T C C A T G G T T A A G G A G A G A T G G G A G A C A T C A T T C T G T T A T A C T T C T G T A C
2050 2060 2070 2080 2090 2100 2110 2120 2130 2140 2150 2160
2070 2080 2090 2100 2110 2120 2130 2140 2150 2160 2170 2180
A C A G T T A T A C A T G C T A T C A A A C C C A G A C T T G C T T C C A T A G T G G G A C T T G C C T G A A A A G T T T G G G G A A A A G T T T C T T T C A G A G A G A T T A
2190 2200 2210 2220 2230 2240 2250 2260 2270 2280 2290 2300
2210 2220 2230 2240 2250 2260 2270 2280 2290 2300 2310 2320

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AGT TATTTTATATATAAATATATATAAAATATATTAATATATCAATATATATATATATGCTGTGTGCTGTGTACACACACCGCATCACACATATATGGAGCAATA
2170 218C 219C 220G 221G 222G 223G 224G 225G 226G 227G 228G

GC.CATTCTAAGACCTTGATGCTTATGAGGCTCGACTAGGCATGATTTGACGAAGCAAGATTGGCATATCATTTGTAACATAAAAAAGCTGACATTGACCCAGACATATTGTACTCTTC

TAA	2419
AAA	2420
AATA	2421
ATTAAT	2422
CTAACG	2423
AAAAAG	2424
ACCAAC	2425
GTTTGG	2426
CAATCT	2427
TACAGC	2428
TAGAGC	2429
TTGAGG	2430
AAGAATT	2431
CAACAGT	2432
TGTCTTC	2433
CAGCAGT	2434
GTTCAG	2435
AGCCAA	2436

AGAGTTGAAGTTCCTAGACCAGGACATAGTATCATGTCTCCTTTAACTAGCATACCCGAAGTGGAGAGGGTGACGCTCAAAGGCATAAGTCATTTCCAAATCAGCCAACTA

AGTGTCTCTTTTCIGCTTTCGTTCACCATGGAACTTTTCATTATAGTTAATCTTCTATCTTGAATCTTCTAGAGAGTTCCTGACCAACTGACGATGTTTCCCTTTGTGAATTAA

AAACGGTCTTCGGTTCATA
2770

Fig. 10

Fig. 11

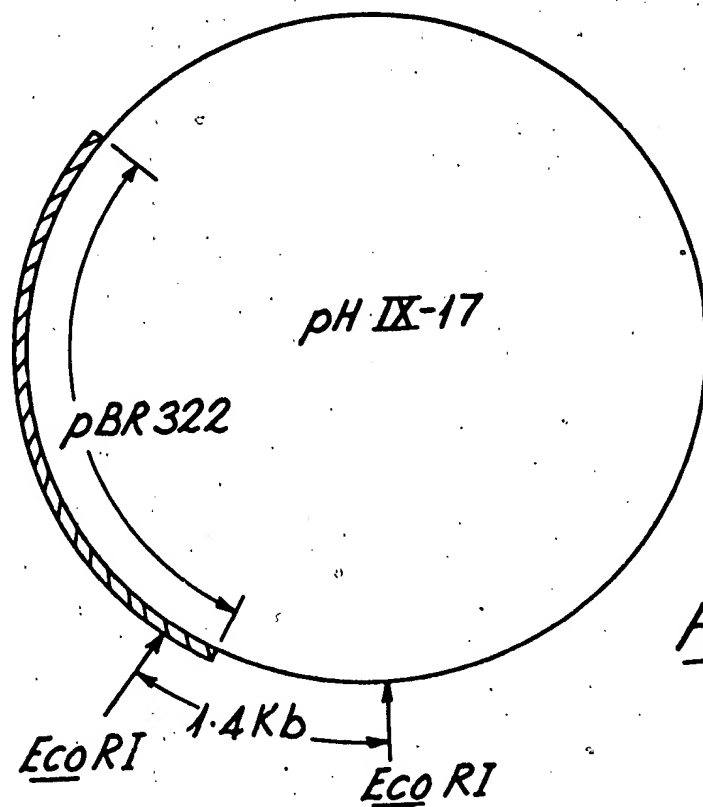


Fig. 12

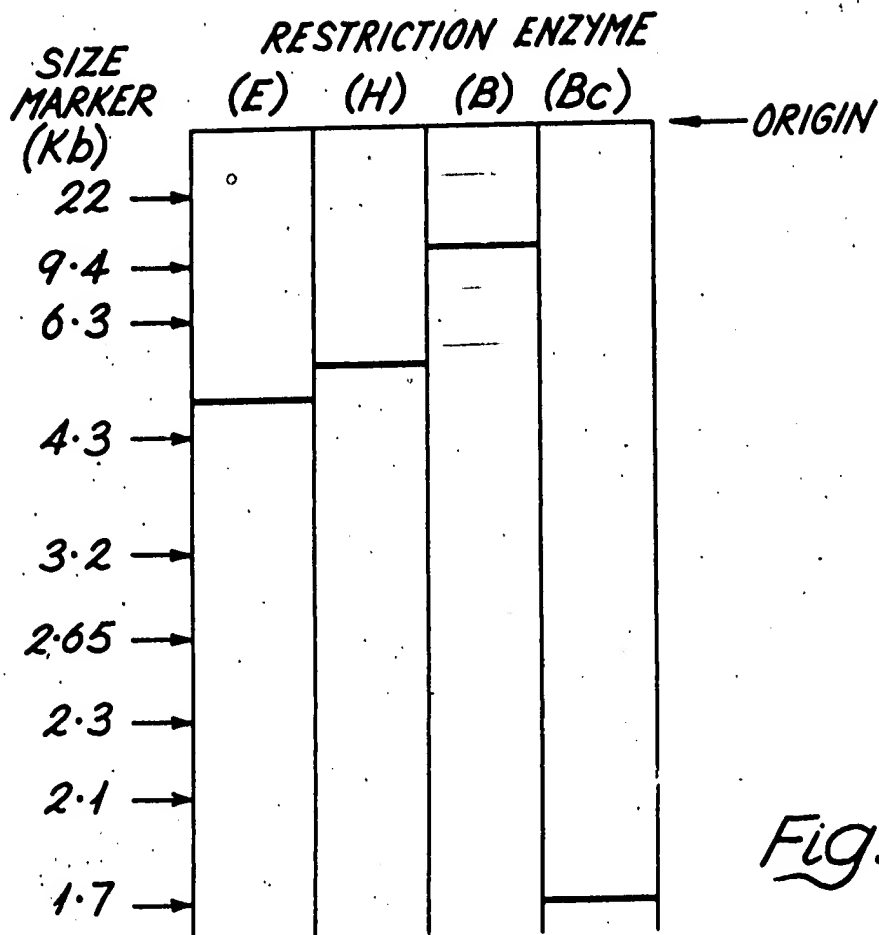


Fig. 13

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